IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	
GUERIN-MARCHAND ET AL	Group Art Unit: 1645
Serial No.:09/837,344	Examiner: N. Minnifield
Filed: April 19, 2001	
For: PEPTIDE SEQUENCES SPECIFIC FOR THE HEPATIC STAGES OF P. FALCIPARUM BEARING EPITOPES CAPABLE OF STIMULATING THE T LYMPHOCYTES	

1.132 DECLARATION

Hon. Commissioner of Patents
P.O. Box 1450
Alexandria, Virginia
22313-1450

Considered
8/8/05
MM

I, Pierre Druilhe do hereby declare the following:

(1) I am currently the director of the Biomedical Parasitology Unit at Institut Pasteur in Paris, France and have been the director of this department for many years. As can be seen from my attached *Curriculum Vitae*, I have published 260 articles and have 10 U.S. Patents issued in my name. I am one of the inventors of the above-captioned U.S. patent application.

(2) I have read the last U.S. Official Action dated February 10, 2005, for the above-identified patent application. It is my understanding that the Examiner deems that the claims directed to vaccines cannot be produced by a scientist using the disclosure of the above-captioned specification since the specification does not teach a scientist how to obtain a malaria vaccine. It appears that the Examiner's reasoning in maintaining this rejection is that the specification purportedly only describes the construction of a Genomic DNA Library and the

provides further immunological testing of the chosen clones, as well as conclusions reached by this testing. I respectfully disagree with the Examiner for the following reasons.

(3) The specification clearly describes immunological responses of subjects exposed to malaria. More specifically, the immunization of mice with the LSA-R-NR proteins and LSA-R peptides of mice of different haplotypes with peptides LSA-R, LSA-J and LSA-NR and responses of the lymphocytes of subjects exposed to malaria indicated that a T-epitope existed in the LSA-R peptide, as well as a B epitope. Other results with more than 500 individuals exposed to malaria should that this T epitope was recognized by the antibodies of about 95% of the subjects studied in Senegal, Leppervoln, Madagascar and Kenya. Responses of lymphocytes obtained from 5 adult African subjects exposed to malaria and more than 200 adult African subjects confirmed that a T epitope of the LSA molecule was defined by the amino acid contained in the synthetic sequence of the peptide LSA-NR.

(4) Lymphocytes of chimpanzees, which were immunized using the LSA-R-NR recombinant protein (SEQ ID NO:19) , confirmed that this protein contained a T epitope. In this regard, the chimpanzees were immunized at 15 day intervals and production of antibodies specific for LSA-R-NR was demonstrated. 60% of the lymphocytes were of the CD8+ phenotype, which corresponds to cytotoxic T lymphocytes.

(5) The specification also discloses studies on mice that were injected with the recombinant protein LSA-R-NR and proof of B epitopes in the LSA-R-NR protein. Further studies conducted in sera taken from 120 African subjects confirmed that the peptide LSA-NR has a B epitope and that this epitope was recognized by 65% of the subjects.

(6) The specification also discloses that chimpanzees were immunized with LSA-R-NR and then further injected with an intravenous injection of 28 million sporozoites of *P. falciparum*. Control chimpanzees in which no immunization occurred were also inoculated in the same manner. Liver biopsies of the immunized chimpanzees were taken on the 6^{th} day after infection. The biopsies of the immunized chimpanzees showed the existence of cellular reaction, lympho-monocytic, around

the hepatic schizonts, infiltrating the schizonts and capable of destroying them. Such images were not observed in the control group.

(7) The cytolytic capacity of the lymphocytes on the immunized chimpanzees in paragraph (6) was further analyzed using a chromium 51 label. The results illustrated that the T epitopes are capable of activating cytolytic T lymphocytes for the LSA-R-NR sequence.

(8) Thus, for the results obtained in the above paragraphs (3) to (7) the following was concluded about the LSA-R-Nr (536) polypeptide:

(a) that this polypeptide is recognized by antibodies originating from subjects with malaria;

(b) that this polypeptide is recognized by sera of chimpanzees immunized therewith;

(c) that this polypeptide induces the function of antibodies (B epitopes);

(d) that this polypeptide induces proliferative responses of T lymphocytes indicating the presence of T epitopes in both chimpanzees and man;

(e) that the polypeptides NR and TER include a major T epitope and a B epitope for man as well as for mouse and the chimpanzee.

(9) Further studies were undertaken with Aotus monkeys confirming the presence of these B and T epitopes and the good antigenicity, as demonstrated in Perlaza et al, Infection and Immunity July 1998 p. 3423-3428, previously of record. In fact this paper indicates that in various types of monkeys such as *Aotus*, *Saimiri* and *Cebus* monkeys liver schizogony can be obtained with *P. falciparum* strains without the need for previous adaptation to these monkeys. Thus, this animal model can be used for preclinical development of pre-erythrocytic malaria vaccines.

(10) Therefore, since the peptide LSA-R-NR (SEQ ID. NO:19) contains both T and B epitopes, larger sequences such as those of SEQ ID Nos 39-42 and 43-46, which contain the LSA-R-NR sequence also contain both T and B epitopes.

(11) Thus, the present specification clearly demonstrates that several polypeptides obtained by the methods in the specification have T epitopes, B epitopes or both and thus induce a wide range of immune responses.

(12) It appears that the Examiner has taken a strict interpretation of the word "vaccine" since at page 6 of the Official Action, the Examiner states that "the definition of a vaccine is a product that provides protection (prophylaxis) against infection, in this case protection against malaria." However, it is well known that a vaccine can either block the effects of the pathogen toxins or prime the immune system against the pathogen such that infection is brought under control more quickly. The latter is done through the vaccine's capability to stimulate antibody (B cells) and T cell responses that can then respond quickly to infection and prevent the pathogen from causing clinical illness.

(13) Indeed, vaccination works by producing T cell and B cell responses. Thus, when vaccinated cytotoxic T cells are produced by the immune system which recognizes the diseased cells and helper T cells assist in activating killer T cells and stimulate B cells, thus producing a cell-mediated immune response. The B cells secrete antibodies which attack malaria, thus producing a humoral immune response.

(14) Thus, it can be concluded that by discovering polypeptides having T epitopes and B epitopes as set forth in the present specification, a skilled artisan can produce a vaccine composition based on the disclosure of the specification. Indeed, I come to this conclusion, since additional studies have been made with LSA-1 antigens in endemic areas since the filing of the present patent application which have linked the LSA-1 antigen with protective immunity. More particularly B-cell and T-cell epitopes in LSA-1 have been associated with protective immunity as stated in the attached Document 1.

I also declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

28 March 2005

Date

Pierre DRUILHE